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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,061	02/27/2007	Michel Cogne	1169-044	1063

20529 7590 09/03/2009

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
09/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,061	COGNE ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-73* is/are pending in the application.

4a) Of the above claim(s) *60-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's provisionally election with traverse of Group I, claims 36-59, is acknowledged. The traversal is on the ground(s) that the application is a 371 application entering U.S. national stage while the partitioning of the claims have not use the lack of unity standard but U.S. application standard. The applicant also asserts that there is no serious burden to examine all claims. The argument has been carefully considered but not found persuasive for the following reasons:

As an initial matter, it is noted the restriction requirement was done in the form for a 371 application.

It is also noted under 35 U.S.C. 372(b)(2), "IN CASE OF INTERNATIONAL APPLICATIONS DESIGNATING BUT NOT ORIGNINATING IN, THE UNITED STATES…THE COMMISSIONER MAY CAUSE THE QUESTION OF UNITY OF INVENTION TO BE REEXAMINED UNDER SECTION 121 OF THIS TITLE, WITHIN THE SCOPE OF THE REQUIREMENTS OF THE TREATY AND THE REGULATIONS;…" Therefore, what was done in the PCT stages is not binding in the national stage.

37 CFR 1.475 (a) recites "AN INTERNATIONAL AND A NATIONAL STAGE APPLICATION SHALL RELATED TO ONE INVENTION ONLY OR TO A GROUP OF INVENTIONS SO LINKED AS TO FORM A SINGLE GENERAL INVENTIVE CONCEPT ('REQUIREMENT OF UNITY OF INVENTION'). WHERE A GROUP OF INVENTIONS IS CLAIMED IN AN APPLICATION, THE REQUIREMENT OF UNITY OF INVENTION SHALL BE FULFILLED ONLY WHEN THERE IS A TECHNICAL RELATIONSHIP AMONG THOSE INVENTIONS INVOLVING ONE OR MORE OF THE SAME OR CORRESPONDING **SPECIAL TECHNICAL FEATURES**." The expression "special technical features" shall mean those technical features that define a

contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant case, the inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT 13.2, they lack the same or corresponding special technical features because as shown in the rejections below, none of the cited art discloses a method of treating cancer. Hence, the asserted special technical features does not define a contribution as a whole over the prior art of record. Consequently, the special technical feature which links claims 36-73 does not provide a contribution over the prior art as a whole, so unity of invention is lacking and restriction is appropriate.

37 CFR 1.475 (b) states "AN INTERNATIONAL OR A NATIONAL STAGE APPLICATION CONTAINING CLAIMS TO DIFFERENT CATEGORIES OF INVENTION WILL BE CONSIDERED TO HAVE UNITY OF INVENTION IF THE CLAIMS ARE DRAWN **ONLY TO ONE** OF THE FOLLOWING COMBINATIONS OF CATEGORIES: (1) A PRODUCT AND A PROCESS SPECIALLY ADAPTED FOR THE MANUFACTURE OF SAID PRODUCT; OR (2) A PRODUCT AND A PROCESS OF USE OF SAID PRODUCT; …". However, instantly claimed animals, targeting vectors and antibodies are drawn to multiple products, and multiple processes. 37 CFR 1.475 (b) does not provide for more than one product as a combination of the invention.

Therefore, it is maintained that these inventions are distinct due to their divergent subject matter and are thus, separately classified and searched. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final

action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 36-73 are pending, Claims 60-73 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 36-59 are under current examination.

Specification

The abstract of the disclosure is objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b). The cover page of a PCT publication is no longer acceptable by the Patent publication branch at the USPTO.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-57, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al*. (USP 7,547,817) in view of *Qiu et al*. (Intl Immunol 1999;11:37-46).

Green teaches a transgenic mouse whose genome comprising a human immunoglobulin heavy chain transgene including constant and variable regions and the exon encoding the CH3 domain and a membrane exon, a non-cognate switch region (e.g. the abstract and column 12) relative to the C.sub.H gene (= deleting mouse Sμ, replacing it with a heterologous one from corresponding constant region). *Green* teaches:

> In another embodiment, the human C.gamma.2 coding sequences, including all of the exons for the secreted and membrane-bound forms of the C.sub.H gene are replaced by another human C.sub.H gene. In this way, the human S.gamma.2 sequences control CSR from C.sub..mu. to the downstream C.sub.H gene. It is known that the hSg2 sequences are stable in yH1C while other human S sequences, some of which have longer tandem arrays of S repeats may be less stable. It is also known that CSR in transgenic mice with the human C.gamma.2 gene is efficient and generates high serum levels of human IgG2 and results in efficient production of fully human IgG2 mAbs. Thus, it may be preferable to retain the human S.gamma.2 with their favorable stability and in vivo response to antigen challenge while engineering CSR to occur to another isotype, e.g., either C.gamma.1 or C.gamma.4. To accomplish this, a vector with the following elements would be constructed: 5' homology located between human S.gamma.2 and the human C.gamma.2 coding exon 1, a human CH gene other than C.gamma.2, the mouse 3' enhancer, a yeast selectable marker, and 3' targeting homology in the YAC arm for example. (Emphasis added)

Here, the recited C.sub.H gene apparently includes Cα IgH locus.

Green further teaches the transgenic mouse comprising a gene encoding human Ig kappa light chain (see e.g. claims 1, 2 and figure 1). *Green* teaches using the transgenic mouse for producing [any] desired specific isotypes of human antibodies, wherein the endogenous IgH loci were inactivated (e.g. claim 3).

Green also teaches a targeting vector and ES cells comprising the vector, wherein the vector comprises the human IgH transgene composed of 66 VH, all the D and J elements, Cμ, Cδ, all regulatory elements, and all in germline configuration (column 10), which would include the heavy chain promoter. The vector also comprises intronic Eμ upstream, and palindrome hs3a/hs1,2/hs3b downstream (column 13), loxP sites and flanking (mouse) sequences of 5'- and 3'-targeting homology for homologous recombination (e.g. column 15). *Green* also teaches introducing the targeting vector into mouse ES cells (e.g. example 27), and breeding to homozygosis (e.g. example 29).

Green differs from instant claimed in that the exemplified target IgH gene is not Cα. However, *Green* contemplates that the invention may provide transgenic mice for producing any desired isotypes of human antibodies including IgA.

Qiu supplemented *Green* by establishing the interest/motivation on producing Cα transgenic mouse. *Qiu* teaches a transgenic mouse whose endogenous switch region and Cα region was replaced with a human Sα and Cα (e.g. fig. 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mouse taught by *Green* by replacing the mouse Sμ with any constant region of interest including Cα of human IgA as taught by *Green* in view of *Qiu* to arrive at instantly claimed invention. Given the levels of the

skilled as illustrated by *Green* in view of *Qiu*, one would have had a reasonable expectation of success.

It is noted that *Green* does not teach the specific genomic organization as recited in claim 52. However, given the levels of the skilled in the art, the limitation falls within the bounds of experimental preference and optimization in the absence of evidence to the contrary.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al*. (USP 7,547,817) in view of *Qiu et al*. (Intl Immunol 1999;11:37-46) as applied to claims 36-57, 59 above, further in view of GeneBank AC073553 (September 2002).

The teaching of *Green* in view of *Qiu* does not specifically mention the sequences as indicated as SEQ ID Nos: 7 & 8.

However, the sequences were available in the art at the time of the priority date. Accordingly, it would have been obvious for the skilled intending to make a human IgH Ca transgenic mouse to use the available sequences as flanking sequence of the targeting vector. Given the knowledge of the skilled in the art, the claimed invention was prima facie obvious in the absence of evidence to the contrary.

Claims 36 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al*. (USP 7,547,817) in view of *Qiu et al*. (Intl Immunol 1999;11:37-46) as

applied to claims 36-57, 59 above, further in view of *Harriman et al.* (J Clin Invest 1996;97-477-85).

These claims read on an embodiment wherein the genome of the transgenic mouse lacks any switch sequence. The combined teaching of *Green* in view of *Qiu* teaches a transgenic mouse with a non-cognative S region in its genome but not lacking a Sμ.

Harriman supplemented *Green* in view of *Qiu* by establishing that it was known in the art the Sμ region is not required for IgA class switch, and that a mouse without the genomic Sμ region still can produce IgA antibody.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mouse taught by *Green* in view of *Qiu* by deleting the Sμ without replacing it with a human Sm as taught by *Harriman* to arrive at instantly claimed invention. Given the levels of the skilled as illustrated by *Green* in view of *Qiu* and Harriman, one would have had a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-51, 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims embrace any transgenic non-human mammal (beyond mouse) having a modified IgH locus. The specification discloses a transgenic mouse comprising a human IgH locus by replacing a mouse switch sequence with a human Cα gene made by homologous recombination using mouse embryonic stem (ES) cells, which require the knowledge of sequences of IgH locus for the genus of non-human mammal, which were not known in the prior art nor taught by the specification.

An adequate written description for a genus of IgH locus requires more than a mere statement that it is part of the invention; what is required is a description of the sequences themselves. With respect to method claims, adequate description of the methods first requires an adequate description of the materials, i.e. a genus of IgH, which provides the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the genus of IgH locus. Therefore, only the described mouse IgH meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 36-51, 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for providing a transgenic mouse comprising a modified IgH locus as claimed, does not reasonably provide enablement for any non-human transgenic mammal comprising a modified IgH locus as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the

art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

To the extent that the essential materials used in the claimed method are not adequately described by the instant disclosure, claims 36-51, 59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, which is not conventional in the art.

The claims embrace any transgenic non-human mammal (beyond mouse) having a modified IgH locus. The specification discloses a transgenic mouse comprising a human IgH locus by replacing a mouse switch sequence with a human Cα gene made by homologous recombination using mouse embryonic stem (ES) cells. With respect to ES cells, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and only "putative" ES (ES-like) cells exist for other species (see *Moreadith et al.*, **J. Mol. Med.** 1997;75(3):208-16, e.g. S*ummary*). Note that "putative" ES cells lack a demonstration of giving rise to germline tissue (germline transmission) or the whole animal (totipotency), a demonstration which is an art-recognized property of ES cells. Such a demonstration has not been provided by the

specification or the prior or post-filing art with regard to the generation of any non-human mammal ES cells, other than the mouse. Without germline transmission, breeding to homozygosity would be impossible. Accordingly, the claims appear to be only enabled for mouse. *Mullin et al*. supports this observation as they discuss the generation of non-mouse transgenics, *Mullins et al*. (**Journal of Clinical Investigation**, 1996) report that "ALTHOUGH TO DATE CHIMERIC ANIMALS HAVE BEEN GENERATED FROM SEVERAL SPECIES INCLUDING THE PIG, IN NO SPECIES OTHER THAN THE MOUSE HAS GERMLINE TRANSMISSION OF AN ES CELL BEEN SUCCESSFULLY DEMONSTRATED. THIS REMAIN A MAJOR GOAL FOR THE FUTURE AND MAY WELL REQUIRE THE USE OF NOVEL STRATEGIES WHICH DEPART WIDELY FROM THE TRADITIONAL METHODS USED IN THE MOUSE" (page 1558, column 2, first paragraph). Moreover, although the specification teaches methods to generate transgenic mice whose genome comprising a human IgH Cα gene, the specification fails to teach methods of generating any other transgenic animals. It was known in the art, just murine subgenus of animal genus encompasses more than 1383 species of rodents, and one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic animals for the breadth claimed.

Without homologous recombination in ES cells, the animal has to be made through microinjection of fertilized eggs, and somatic cell nuclear transfer. It was highly unpredictable whether one could make the genus of modified IgH animals, wherein the animal producing human IgA antibodies. This is because the aforementioned techniques were still under-development, and highly unpredictable.

The process of pronuclear microinjection is highly inefficient at the time of the filing. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome, which would vary among different species of animals. The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994 J. Biotech. 34, page 281). Moreover, *Mullins* (**J Clin Invest**, 1996;97:1557-60) teaches, the major problems regarding pronuclear microinjection is that the exogenous DNA integrates randomly into chromosomal DNA, and that mouse-derived agents do not adequately prevent differentiation of stem cells in species other than mouse (left column, page 1558). *Mullins* concludes that "THE USE OF NONMURINE SPECIES FOR TRANSGENESIS WILL CONTINUE TO REFLECT THE SUITABILITY OF A PARTICULAR SPECIES FOR THE SPECIFIC QUESTIONS BEING ADDRESSED, BEARING IN MIND THAT A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER." (page S39, Summary). *Wall* (J Dairy Sci 1997;80:2213-24) states that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph).

The same is true for somatic cells nuclear cell transfer cloning. For example, *Denning* (Nat Biotech 2001;19:559-562) teaches difficulties of somatic cell cloning, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF

GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560). The unpredictability also lies with the faulty epigenetic reprogramming in nuclei cloning. Since the applicants have not disclosed other animal species encompassed by the claims, it is highly unpredictable of the outcome of the recited method in making any animal. *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches, at a post-filing date, that "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Yanagimachi* goes on to teach, "THIS LOW EFFICIENCY OF CLONING SEEMS TO BE DUE LARGELY TO FAULTY EPIGENETIC REPROGRAMMING OF DONOR CELL NUCLEI AFTER TRANSFER INTO RECIPIENT OOCYTES. CLONED EMBRYOS WITH MAJOR EPIGENETIC ERRORS DIE BEFORE OR SOON AFTER IMPLANTATION" (abstract). *Wilmut* (Cloning Stem Cell 2003;5:99-100) teaches, "BY THE TIME OF DOLLY'S DEATH IN 2003, CLONES HAD BEEN DERIVED FROM ADULT CELLS OF SEVERN MAMMALIAN SPECIES, BUT THE SAME TECHNIQUES WERE NOT SUCCESSFUL IN SEVEN OTHERS, DESPITE INTENSIVE EFFORTS BY EXPERIENCED RESEARCH TEAMS. THESE INCLUDE RHESUS MONKEY, RAT, DOG, AND HORSE. THIS FAILURE EMPHASIZES THE IMPORTANCE OF DIFFERENTCES BETWEEN SPECIES. THE DIFFERENCE MIGHT BE IN THE MOLECULAR MECHANISMS THAT REGULATE EARLY DEVELOPMENT OR IN ENABLING TECHNIQUES FOR OOCYTE RECOVERY, EMBRYO CULTURE, OR EMBRYO TRANSFER. SUCH DIFFERENCES HAVE ALREADY BEEN IDENTIFIED BETWEEN THE SPECIES FROM WHICH CLONES HAVE BEEN DERIVED", and "THE MOST STRIKING THING ABOUT THE

TECHNIQUES THAT EMERGED DURING DOLLY'S LIFE IS THAT MAMMALIAN CLONING REMAINS A REPEATABLE, BUT INEFFICIENT PROCEDURE…AN EXTRAORDINARY VARIETY OF ABNORMALITIES HAVE BEEN DESCRIBED IN CLONED EMBRYOS, FETURESES, AND OFFSPRING".

Polejaeva et al (Nature 2000;407:86) teach, "TO DATE, THE EFFICIENCY OF SOMATIC CELL NUCLEAR TRANSFER, WHEN MEASURED AS DEVELOPMENT TO TERM AS A PROPORTION OF OOCYTES USED, HAS BEEN VERY LOW (1-2%). A VARIETY OF FACTORS PROBABLY CONTRIBUTE TO THIS INEFFICIENCY THESES INCLUDE LABORATORY TO LABORATORY VARIATION, OOCYTE SOURCE AND QUALITY, METHODS OF EMBRYO CULTURE, DONOR CELL TYPE, POSSIBLE LOSS OF SOMATIC IMPRINTING IN THE NUCLEI OF THE RECONSTRUCTED EMBRYO, FAILURE TO REPROGRAM THE TRANSPLANTED NUCLEUS ADEQUATELY, AND FINALLY, THE FAILURE OF ARTIFICIAL METHODS OF ACTIVATION TO EMULATE REPRODUCIBLY THOSE CRUCIAL MEMBRANE-MEDIATED EVENTS THAT ACCOMPANY FERTILIZATION" (1st paragraph). Apparently, it was not, and has yet to become routine in the art to obtain a nonhuman transgenic livestock such as a transgenic pig having human Cα and producing human IgA. The skilled in the art intending to practice the claimed invention would have to carry out undue experimentation to make the claimed non-human transgenic mammals while the efficiency of the process would be expected low (<=1%) and phenotypic outcome of the mammal is unpredictable due to the many variant factors as discussed *supra*.

Accordingly, in view of the state of the art and the quantity of experimentation necessary for making any human IgH Cα transgenic non-human mammal producing a human IgA, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to any transgenic non-human animal whose genome comprises a homologous disruption of endogenous *IgH* gene and a transgenic

human IgH Cα, and the breadth of the claims, other than the exemplified mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is vague and indefinite because it is unclear which subject the phrase "comprising at least..." defines. Inserting “wherein the transgene” before “comprising” may obviate this rejection.

Claim 46 recites the limitation "the inactivated kappa chain". There is insufficient antecedent basis for this limitation in the claim.

Claim 48 recites the limitation "the inactivated J chain". There is insufficient antecedent basis for this limitation in the claim.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
September 3, 2009